Does non-adherence increase treatment costs in schizophrenia?

Mark Pennington*[1], Paul McCrone[1].

King's Health Economics
PO24 David Goldberg Centre
Institute of Psychiatry, Psychology & Neuroscience
King's College London
De Crespigny Park
London SE5 8AF
Tel: 020 7848 0589
Fax: 020 7848 0458
mark.w.pennington@kcl.ac.uk
http://www.kcl.ac.uk/khe

Word count: 4,767

Running title: schizophrenia costs and non-adherence

Key words: schizophrenia, relapse, antipsychotics, cost, adherence, discontinuation

Mark Pennington ORCID: 0000-0002-1392-8700

Paul McCrone ORCID: 0000-0001-7001-4502

This study was funded by Janssen-Cilag Ltd. It was not part of a specific programme. Representatives from Janssen have commented on a draft but the authors retained sole control over the design, implementation and reporting of the results. MP reports no conflicts of interest. PM reports no conflicts of interest.

Abstract

Introduction

Medication non-adherence is a serious barrier to treatment of schizophrenia. Understanding the impact of non-adherence on costs is essential to the assessment of the cost-effectiveness of interventions in which adherence to treatment is a concern.

Objectives

We undertook a comprehensive review of the available literature on the impact on costs of non-adherence to antipsychotics in the treatment of schizophrenia.

Methods

We performed a search on multiple databases (MEDLINE, Embase, PsycINFO and Health Management Information Consortium) for any study reporting the impact of adherence to antipsychotics on costs in patients with schizophrenia up to February 2018. We included trials of behavioural interventions but excluded comparisons of different pharmacological therapies. Studies were included if at least one third of the study population had schizophrenia and costs were reported.

Results

Thirty-four publications on 28 studies met the inclusion criteria. Twenty studies reported analyses of administrative databases, primarily Medicaid. Findings on health care costs were mixed but suggested that lower pharmacy costs in non-adherent patients may outweigh increased hospitalisation costs where drug costs are relatively high. A few studies published analysis of prospective cohort data, or trials of behavioural interventions intended to influence adherence, mainly in a European setting. Findings were again mixed but indicate that increasing adherence does not reduce overall costs.

Conclusions

Inference from analysis of administrative data is limited by the risk of selection bias. Inference from trials is limited by small sample sizes. The literature does not consistently support an assumption that non-adherence increases health care cost.

Key points

- An assumption prevails that non-adherence increases treatment costs for schizophrenia due to increased risk of hospitalisation
- The available evidence suggests that decreases in other costs, primarily pharmacy costs in the US, may offset increased hospital costs arising from non-adherence
- There is insufficient evidence to conclude which direction health care costs change with decreasing adherence; an assumption of no change is more defensible than an assumption that costs rise

1. Introduction

Schizophrenia is a life-long condition characterised by frequent relapses during which patients exhibit psychotic symptoms [1]. These psychotic episodes are often severe enough to necessitate stabilisation and treatment in psychiatric hospitals, and schizophrenia patients are likely to be hospitalised many times during their lifetime. Treatment with antipsychotics can reduce the frequency of relapse, offering the potential to reduce the high costs of managing schizophrenia patients [2]. However, antipsychotics are associated with severe side-effects including weight gain, development of diabetes and movement disorders [3]. The side-effects of treatment and the extent to which patients may lack insight into their disease contribute to high treatment switching and discontinuation rates [4]. Reported compliance rates range from 20% to 72% for schizophrenia patients [5]. Many patients are partially compliant and may take 'treatment holidays' of varying duration. Hence non-adherence may manifest itself as a gap in medication or partial fill of prescriptions.

Measuring compliance is challenging. Patient and physician reports are subjective and both parties may have a tendency to exaggerate compliance [6,7]. Pharmacy records are objective but are also likely to overestimate compliance since not all prescribed medication will be consumed. Individuals who fill at least 80% of prescriptions are generally considered to be adherent and those who fill between 50% and 80% are generally considered partial adherent [8]. Measures of compliance based on records of prescription fills are most commonly quantified as the Medication Possession Ratio (MPR) - the number of days of medication supply in the index period divided by the number of days in the index period (often 365) [9]. Variations include the Proportion of Days covered which is equivalent to the MPR with values capped at 1. In a comparison of eight measures of adherence, lower adherence on all measures was associated with a higher risk of hospitalisation amongst schizophrenia patients, and MPR and PDC were the best predictors of hospitalisations, but the differences between measures were small [10].

A number of studies have reviewed the literature around the causes and consequences of, and interventions to reduce non-adherence [11-19]. These reviews and other evidence [20,21] point to a consensus that non-adherence leads to greater risks of poor functional outcomes including relapse and associated hospitalisation, suicide and violent behaviour. Whilst the side-effects of medication can themselves be a cause of hospitalisation there is strong evidence to indicate increased hospitalisation associated with non-adherence [12,17]. Early studies of both intermittent treatment and tapered discontinuation demonstrated both were associated with increased hospitalisation rates [22,23].

Hospital stays are expensive and likely to be increased in poorly adherent patients. However, non-adherence may reduce the cost of drug treatment which can form a sizable proportion of total treatment costs in the US. Hence the impact on overall costs is less obvious. An early review of the literature concluded that 'a definitive relationship exists between compliance and the economic costs of schizophrenia' [19]. However, that review included studies published prior to 2003, most of which were primarily intended to compare drug treatments. More recent reviews have concluded there is a link between non-adherence and hospitalisation, but have failed to find a link between adherence and overall costs [12,13]. This paper reviews the literature relating to the costs associated with non-adherence and discontinuation of treatment and reappraises the evidence regarding the impact of non-adherence on costs.

2. Methods

A structured search of MEDLINE, Embase, PsycINFO and HMIC Health Management Consortium was undertaken on 27th February 2018 for articles reporting on the cost of adherence or discontinuation of treatment for schizophrenia. The search algorithm (provided in the appendix) included the following in the title, abstract or keywords: cost$, schizophrenia, recidivis$, non-complian$, noncomplian$, complian$, continu$, discontinu$, non-adheren$, nonadheren$, adheren$, cessat$, cease$, stop$, recidivis$. Citations of all identified relevant articles were also searched and references checked. We applied the following inclusion criteria:

1. Publications in English
2. Over one third of the study population diagnosed with schizophrenia or schizoaffective disorder
3. The study reported costs
4. Trials of interventions to modify adherence which included a comparison of costs

Studies reporting only the impact on hospitalisation rates were excluded. Modelling studies and reviews were excluded. Conference abstracts were included if they reported the impact of adherence on costs. We included trials of behavioural interventions designed to modify compliance where such trials reported a difference in adherence which was significant at the 5% level, but excluded trials comparing different pharmacological therapies. Observational studies analysing the impact of adherence on costs were included regardless of the original purpose of recruitment (e.g. trials which failed to demonstrate an impact on adherence). We extracted data on the impact of adherence on the costs of hospitalisations, pharmacy costs and total costs where these were available. Where data are reported both unadjusted and adjusted for patient characteristics we report the adjusted data.

The quality of the evidence from included studies was assessed using the following criteria selected to highlight aspects of design or reporting relevant to the research question:

- reporting of price year
- assessment of adherence using more than one source
- assessment of compliance in the period prior to costs rather than concurrently
- identification and separate analysis of patients over filling prescriptions
- identification and separate analysis of patients switching or augmenting medication
- use of study design or regression analysis to control for confounding on observed patient characteristics
- use of study design or regression analysis to control for confounding on *unobserved* patient characteristics.

3. For each criterion, studies were assessed as meeting the criterion, not meeting the criterion or unclear where insufficient reporting prevented assessment.Results

The electronic database search identified 1932 publications after removing duplicates. After initial screening, 152 original publications were retained (Figure 1). On examination, 27 publications met the inclusion criteria. A further 4 studies were identified through searches of references and

citations and supplementary information on included studies was obtained from 3 additional publications. In total, 34 publications on 28 studies met the criteria and were included in the review. The majority of the relevant literature originated from the US and presented analysis of administrative databases in which prescription fill data were used to identify patients with a medication gap (Table 1). There was a small body of literature reporting economic evaluations alongside clinical trials. Three of the four trials were of interventions to boost adherence; only one trial randomised patients to discontinuation of therapy. Patients were generally recruited in an outpatient setting and adherence was assessed by patient questionnaire or physician interview. Finally, we included four analyses of the impact of adherence on costs based on survey data or prospective cohort studies, of which some were recruited for a randomised trial.

3.1 Analysis of administrative databases

Twenty studies reported on analyses of administrative databases [24-43] of which 17 were US based [24-40] and 13 analysed Medicaid data [24-36]. A conference abstract provided additional cost data for one of the studies [44]. Sample sizes varied from 354 to 87,015. Most studies excluded patients with gaps in eligibility or enrolment status of 1-2 months or more, institutionalized patients, and patients on depot medications for whom treatment is generally administered by a clinician. Adherence was most often quantified as the MPR. The scope of these studies was generally limited to health care costs and some studies considered only hospital and pharmacy costs. Two studies contrasted the impact of adherence on mental and physical health care costs [26,40] and one study included criminal justice costs [27]. The complexity of these studies ranged from simple comparisons of costs across patient groups categorised by compliance to a sophisticated analysis of longer term costs which controlled for endogeneity using instrumental variables. Follow-up periods over which costs were assessed were commonly a year with some studies assessing compliance in a prior index period (of typically one year's duration).

3.1.1 Unadjusted comparisons across adherence groups

Nine studies examined the impact of adherence on costs without explicit consideration of medication switching, augmentation or excess filling [24-27,37,38,40-42]. All except one evaluated adherence and costs over the same period; one study evaluated the impact of adherence in the first year on costs in the second [40]. Most report comparisons of cost data without controlling for differences in patient characteristics although one publication matched patients according to length of follow-up and type of insurance [40]. Four publications undertook multivariate regression modelling of costs [24-26,40]. The study by Svarstad and colleagues was notable as the only study which assessed adherence from more than one data source [24]. In two studies non-adherence was qualified as a treatment gap [38,41], and one study characterised adherence according to the number of complete years with outpatient elective psychiatric care and/or PDC>0.5 [42]. One study examined adherence to antipsychotics and to cardio-metabolic medication in 87,015 Medicaid patients with schizophrenia and cardio-metabolic comorbidities [25]. Robertson et al. examined the impact of adherence in the three months following discharge from psychiatric hospital on healthcare and criminal justice costs [26].

Six of the seven studies reporting hospital costs found a reduction in hospital costs associated with adherence [24,26,37,38,40,42]. All five studies which reported drug costs found increasing costs associated with adherence [26,27,37,38,42]. With regard to total costs the picture was mixed; three studies found higher costs for adherent patients [25,41,42] and three studies found lower costs

[26,27,38]. A further study which did not report total costs found a reduction in pharmacy costs in non-adherent patients which more than offset the increase in hospitalisation costs [37]. Robertson and colleagues found lower overall costs in non-adherent patients despite the inclusion of criminal justice costs which were higher amongst non-adherent patients [27]. One study undertook separate cost comparisons for patients prescribed typical antipsychotics, atypical antipsychotics or both [25]. Costs rose with increasing non-adherence across all three subgroups of patients. However, the differences were less amongst patients prescribed atypical antipsychotics where drug costs were higher.

3.1.2 Separate analysis of 'switchers' and 'augmenters'

Three studies specifically addressed treatment switching and indicated that amongst adherent patients, those switching or augmenting drug therapy have higher costs [28-30]. All analysed Medicaid data. An early study partitioned 2476 patients into those receiving no therapy (17%), and those who delayed treatment (27%), switched or augmented therapy (32%), or maintained initial treatment without delay (25%) [28]. A poster presentation from the same group compared patients 'persistent' with a single therapy to non-persistent patients and patients augmenting their therapy [29]. Both studies applied regression analysis to control for differences in observed patient characteristics across groups. The third study applied latent class analysis to 36,195 Medicaid patients and identified three underlying classes of patients: adherent patients (14%); partially adherent patients (21%) and non-adherent patients (65%) [30]. Treatment switching was rare amongst both adherent patients and non-adherent patients but very common in the partially adherent group.

Two of the three studies reported inpatient and drug costs [28,30]. Inpatient costs were lowest amongst adherent patients. Patients switching therapy had the highest drug costs, non-adherent patients had the lowest drug costs. All three studies reported total costs and found the highest costs amongst patients switching or augmenting treatment. Two of the three studies found lower total costs amongst non-adherent patients compared to adherent patients [29,30]. The third study found lower costs in patients with a treatment gap compared to non-adherent patients but higher costs in patients receiving no drug treatment for their schizophrenia [28].

3.1.3 Separate analysis of 'excess fillers'

Three studies distinguished patients who filled prescriptions in excess of their prescribed treatment (excess fillers) from patients compliant with medication and reported increased hospitalisation risk and higher costs for excess fillers [31,32,43]. Adherence was measured as MPR and excess fillers defined as those with MPR greater than 1.1 to 1.25 across the three studies. All three studies used regression analysis to adjust for differences in patient characteristics across adherence groups and one included a propensity score in the adjustment [43]. Two of the three studies reported inpatient costs, drug costs and total costs from analysis of Medicaid data [31-32]. Both found higher inpatient costs amongst excess fillers and non-adherent patients compared to adherent patients and increasing drug costs with increasing proportion of prescriptions filled. However, only one of the two studies found lower total costs in non-adherent patients compared with adherent patients [31]. The third study reported higher costs in both non-adherent patients and excess fillers compared with adherent patients, but it was unclear whether the costs reported included drugs [43].

3.1.4 Application of quasi-experimental design or statistical analysis to control for unobserved confounding

Three analyses used more sophisticated designs to estimate the impact of non-adherence [33,34,39]. Two of the studies compared adherence and cost data within patients over time to eliminate the impact of time invariant unobserved patient characteristics [33,39]. Both exploited an exogenous shock in the form of an increase in medication copayments falling on patients. Farley compared Mississippi Medicaid data before and after a rise in co-payments with comparator states with minimal co-payments finding the change induced a 5% reduction in compliance and 4% reduction in mental health costs [33]. The change in costs may have been influenced by the simultaneous 5% cut in physician reimbursement introduced with the copayment change. Zeber and colleagues compared trends in hospitalisation rates for 20 months before and after an increase in copayments in 40,654 patients subject to the copayment and 39,983 patients with a military waiver [39]. The copayment rise was associated with a decrease in psychotropic pharmacy fills and a modest but significant increase in hospitalisations. A subsequent conference presentation estimated the cost of the changes in resource use associated with the copayment change and reported cost increases in excess of the revenue from the copayment change [44].

The final study applied two instrumental variables, the copayment rate and the availability of postal medication fills, in a two stage least squares (TSLS) analysis of annual costs for 32,374 Medicaid and commercially insured patients with schizophrenia or bipolar disorder [34]. The TSLS analysis generated results sharply in contrast to the simple linear regression (OLS). Both OLS and TSLS analysis indicated higher annual hospital costs associated with non-adherence and with early discontinuation of therapy. OLS regression indicated an annual total cost (of which hospital costs are one element) *decrease* of $3,071 associated with non-adherence and a similar decrease of $3,705 associated with early discontinuation. In contrast, TSLS analysis indicated a *rise* in annual total cost of $19,497 associated with non-adherence and a rise of $23,927 associated with early discontinuation.

3.1.5 Other studies

Marcus & Olfson estimated the hospital costs attributable to non-adherence in schizophrenia using US population level data [35]. Regression analysis was used to determine the relative risk of hospitalisation associated with non-adherence and the impact on length of stay. Annual hospitalisation costs associated with schizophrenia were estimated at $860million (2005 USD), of which $106million could be attributed to non-adherence. Markowitz and colleagues examined adherence and costs for 2,541 Medicaid patients from six months prior to 12 months after schizophrenia-related hospitalisation [36]. Adherence was defined as MPR ≥ 0.8. Adherence declined from 63% to 46% prior to admission. Adherence rose to 78% in the two months after discharge and then settled back to *circa* 60%. Despite higher adherence, more inpatient admissions occurred in the first two months following discharge compared to the next two months (13.9% vs 8.3%; $p < 0.001$) and schizophrenia related total costs were higher ($2,708 vs $2,102; 2010 USD; $p < 0.001$).

3.2 Cohort studies

Six reports from four cohort studies have published data on adherence and costs (table 1) [45-50]. Three of the studies collected data prospectively [46-48] and one analysed survey data [45]. Adherence was assessed by clinician interview in two of the studies [47,48] and possibly also a third [46], although the method of assessment of adherence was not clearly reported. All studies used

regression analysis to estimate the impact of adherence. Two of the cohorts were recruited to RCTs [46,48]. QUATRO randomised patients in four European cities to adherence therapy or usual care [48]. No significant impact of the intervention on adherence was observed. The MECCA study trialled a computer mediated intervention (DIALOG) to improve patient-clinician communication and found a significant effect of the intervention on quality of life [46].

Two of the four studies reported the impact of adherence on inpatient costs and both reported a rise with non-adherence [45,47] although neither reported a significant difference (at the 5% level). The only study which analysed the impact of adherence on drug costs reported increased costs associated with non-adherence at baseline [46]. Two of the four studies found increasing total costs associated with non-adherence [45,47] and two studies reported total costs decreasing with non-adherence [46,48]; none found the difference in total cost to be statistically significant at the 5% level.

3.3 Trials

Economic evaluations have been published for four RCTs in which the intervention led to a significant change in compliance [51-58] (table 2). Two of the trials tested behavioural therapies to increase adherence [52,56], one trial tested financial incentives [58] and one trial tested guided discontinuation of antipsychotic therapy [54]. All the trials were of modest size. The earliest and smallest trial reported higher costs in the control group at baseline and follow-up, and found no statistically significant differences in cost between treatment and control at the 5% level [51]. More recent trials of adherence therapy and financial incentives reported improved adherence in the intervention arm along with a non-significant (at 5%) increase in costs [55,57]. In the final trial 128 Dutch first episode psychosis patients (45% with schizophrenia) were randomized to guided discontinuation or maintenance therapy [54]. Despite a higher relapse rate, total costs over 18 months following discontinuation were lower in the intervention group, driven primarily by lower hospitalisation costs, but differences were not significant at the 5% level [53]. The maintenance group had higher costs at baseline and a higher proportion of patients with schizophrenia.

3.4 Summary of the evidence

- Adherence lowers hospitalisation costs but increases pharmacy costs
- Evidence of the impact of adherence on total costs from analysis of both administrative databases and cohort studies is mixed
- ‘Switchers’, ‘augmenters’ and ‘overfillers’ cost more than adherent patients, but studies excluding them do not necessarily find adherence is associated with lower total cost
- Evidence of the impact of adherence on total costs from trials and observational studies which controlled for unobserved confounding is also mixed.

3.5 Assessment of methodological quality

Figure 2 presents the results of the assessment of the methodological quality of the analyses of non-randomised studies. There is no indication that the methodological quality of studies has improved over time. Indeed, three of the four studies which met none of the assessment criteria were published after 2012 [37,38,42]. Most studies undertook regression modelling to adjust for baseline differences in patients across comparison groups but many failed to report the relevant year for cost data. Separate comparison of medication switchers and excess fillers is more commonly undertaken in the literature prior to 2013. Some studies addressed the temporal impact of non-adherence on

costs or risk of hospitalisation either by design or during analysis, but very few studies addressed the risk of confounding on unobserved patient characteristics.

4. Discussion

The evidence from the available literature on the costs of non-adherence confirms the link between non-adherence and both hospitalisation rates and hospital costs. The fall in pharmacy costs associated with non-adherence might also have been anticipated, but our review confirms this. The combined impact of these two opposing trends on overall costs is harder to discern. The majority of analyses of US databases have shown a fall in overall costs associated with non-adherence. This may reflect high drug costs in the US combined with relatively short length of stay for hospitalised patients limiting the cost impact of increased hospitalisation. Database analyses from South Korea, Thailand and the Netherlands indicate rising costs with non-adherence. This may reflect lower drug costs relative to inpatient costs in these countries. In contrast to the database analyses the majority of cohort studies and RCTs reported on European populations. Here, again the evidence on the impact of adherence on total costs is mixed, although the majority of more recent studies indicate a rise in total costs with increasing adherence.

The limited number of studies which isolated patients switching or augmenting therapy indicate a tendency for such patients to accrue higher costs than those adherent to a single therapy. Hence inclusion of such patients might be expected to increase the costs for adherent patients. Despite this, those studies which did compare patients adherent to a single therapy with non-adherent patients generally found adherence to be associated with higher overall costs. Patients filling excess prescriptions also incur higher drug costs than patients filling the correct number of prescriptions. The motivation to fill prescriptions for antipsychotics in excess of prescribed treatments are unclear, but may be associated with other lifestyle factors which increase treatment costs [31]. Again, inclusion of these patients with adherent patients is likely to increase the costs for adherent patients. Two of the three studies which isolated excess fillers found lower total costs amongst adherent patients compared to non-adherent patients.

For both augmentation of treatment and excess prescription fills a direct link with increasing drug costs might be expected. It also seems likely that patients who switch or augment treatment have more severe disease than patients who persist with a single therapy, although they may be not be more severe than non-adherent patients. Assuming severity is directly related to costs, incomplete adjustment for case-mix is likely to bias analysis. The scope to adjust for case-mix using observed patient characteristics may be very limited in administrative databases. Results from the single study which controlled for endogeneity using instrumental variables suggest that higher costs amongst adherent patients arise from unobserved differences with non-adherent patients and that after controlling for these differences costs are sharply lower amongst adherent patients [34]. This finding should be treated with caution as simulation studies have demonstrated the sensitivity of TSLS procedures to the strength of the instrumental variables [59].

The experimental and quasi-experimental studies offer the opportunity to examine the impact of adherence on costs with control of unobserved confounding through experimental design. The evidence from the four trials reviewed would suggest that increasing adherence does not reduce costs and may be associated with a modest rise in costs. However, the size of the studies limits

inference from them. The two quasi-experimental studies which exploited a co-payment increase for prescription drugs analysed large samples, but generated conflicting results [33,39]. This small body of literature would suggest costs do not fall with increased adherence after controlling for patient severity.

Our findings suggest that interventions to improve adherence may not deliver cost savings overall. However, improvements in adherence may well deliver benefits to patients and their families. Such a goal ought to be the primary motivation of interventions to improve adherence and may well justify the financial investment.

4.1 Methodological quality of literature

A single study appraisal tool would be limited in its ability to highlight strengths and weaknesses across the diverse types of study in our review. Instead, we chose to examine aspects of study implementation and reporting of particular relevance to our research question, and applicable to all the included studies. Figure 2 highlights a number of limitations, some of which are inherent in the research designs. Inevitably, studies of administrative data rely on prescription records to quantify adherence. An assumption that prescribed medication is consumed is unavoidable, but the failure of most of these studies to isolate 'excess fillers' is an avoidable weakness. Such patients present an increased risk of hospitalisation, as well as increasing pharmacy costs, possibly as a result of unobserved patient characteristics. Identification of the direction of causation and control for selection bias is a challenge for any observational study. Few of the analyses based on administrative data attempted to isolate the temporal pattern of non-adherence and resource use, and only three attempted to control for unobserved confounding across comparison groups [33-35,39]. The dominance of US settings limits the generalizability of the findings from the literature reporting administrative database analyses. The reliance of observational studies on patient reports for assessment of compliance is an avoidable limitation. Exaggeration of compliance may have blunted comparisons across compliance groups; the SOHO study reported high compliance rates (71%) and very modest differences in costs across comparison groups [47,49].

4.2 Comparisons with previous reviews

Four previous reviews have examined the cost of non-adherence and all concluded that non-adherence increases hospital costs, but only one review concluded non-adherence increases total costs. An early review included 12 studies which were predominantly a mixture of observational studies and trials primarily designed to compare different antipsychotics [19]. The authors concluded that lower compliance was associated with higher treatment costs. Dilla and colleagues reviewed eight studies reporting noncompliance and cost data of which four were analyses of Medicaid data and two were reports of mirror-image studies [12]. They modestly concluded that interventions to improve adherence could improve patient quality of life without substantially increasing treatment costs. A review of US studies of hospitalisation costs (7 studies including a mixture of administrative database analyses and modelling studies) found an association between adherence and lower hospital costs [17]. Higashi and coworkers reviewed 12 studies examining the relationship between adherence and hospitalisation [13]. The authors reported a consistent link between non-adherence and hospitalisation risk but did not summarise the evidence on costs.

4.3 Strengths and limitations

This review sought to capture all of the available evidence on the impact of non-adherence on costs, and to provide a balanced perspective on the disparate and often conflicting evidence base. We excluded studies which reported exclusively on the impact of non-adherence on hospitalisation rates where there is ample evidence of a link. Our research question and subsequent search strategy concerned the cost of non-adherence. We included all studies of antipsychotics in psychosis patients in populations with at least some schizophrenia patients and trials of interventions intended to change adherence. Although we searched a limited number of databases, we undertook extensive efforts to search articles cited in and citing relevant retrieved studies to ensure that all relevant publications were captured. We did not apply a formal assessment of quality since the diverse nature of the studies would have been poorly represented by a single measure. Instead we highlight indicators of quality which are relevant to most studies and to the research question.

The preponderance of studies from US settings limits the generalizability of our findings. Whilst the cost of a psychiatric bed day in the US is likely to be higher than in most other settings, typical length of stay is short. Hence overall hospitalisation costs may well be higher in European settings. Pharmacy costs also appear to be higher in US settings. These differences will act synergistically to raise the relative costs of non-adherence compared to adherence in Europe compared with the US. Few studies in our review included costs falling outside health sectors. Whilst costs falling on criminal justice appear to be modest, there are likely to be considerable additional costs associated with relapse which fall on other public sector budgets. The impact of non-adherence on these costs is difficult to predict; evidence from the two large observational, European studies which collected cost data outside health is conflicting [47,48]. Evidence of the impact of non-adherence on productivity costs is lacking, but it seems likely that non-adherence would increase them. Only a handful of studies examined the temporal effect of adherence on costs and those that did typically examined costs in the following 12-18 months. The longer term impact of adherence on costs is poorly studied. A further limitation of the review is the exclusion of patients on depot medication by most studies. The impact of non-adherence in this group may be moderated by greater residual levels of antipsychotics. Finally, it is important to emphasise that this review considered only costs. Increased relapse rates and hospitalisation arising from non-adherence may have a detrimental effect on the quality of life of patients and their relatives.

5. Conclusions

An assumption that overall health care costs rise with non-adherence is not supported by the literature. Indeed, there is some evidence from more recent analyses of US administrative data and a small trial literature to suggest costs fall with non-adherence. Comparisons of costs across adherent and non-adherent patient subgroups in administrative databases are subject to the risk of selection bias. Trials of behavioural interventions intended to manipulate compliance provide an opportunity to circumvent selection bias, but published studies are too small to provide definitive conclusions on the impact of adherence on costs. In the meantime, an assumption that changes in adherence have no overall impact on health care costs, ceteris paribus, may be the most defensible.

6. Acknowledgements

This study was funded by Janssen-Cilag Ltd. It was not part of a specific programme. Representatives from Janssen have commented on a draft but the authors retained sole control over the design, implementation and reporting of the results. PM is responsible for the conception of the project and editing of the manuscript. MP undertook the literature searching, extraction of data and drafting of the manuscript.

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Tables

Reference	Database/ study	Observ-ation Years	No. of pati-ents	Follow-up period	Costs included	Adherence categories considered	Annualised difference in costs between adherence categories[#] (statistical significance)			Price Year and currency	Patients with schizo-phrenia[a]
							hospital	Drugs	total		
Database analysis – comparison of costs between adherent and non-adherent patients											
Svarstad 2001 [24]	Medicaid	'89 –'90	619	1 year	Psychiatric hosp. costs	Some/no quarters without therapy	$2,356**[b]	nr	nr	nr USD	67%[c]
Becker 2007 [25]	Medicaid	'99 –'00	10,330	2 years	Mental health care, some crime[d]	MPR <0.25 vs >=0.75	nr	nr	$2,483[e] (ns)	nr USD	100%
						MPR 0.25-0.499 vs >=0.75	nr	nr	$1,911[e] (ns)		
						MPR 0.5-0.749 vs >=0.75	nr	nr	$522[e] (ns)		
Offord 2013a [37]	Medicare	'05 –'10	354	1 year	All health care	MPR>=0.7; MPR<0.7	$4,031 (ns)	-$3,514***	nr	nr USD	100%
Offord 2013b [38]	US private	'06 –'09	1,462	1 year?	All health care	Time to 30d drug gap of >90d; <90d	$1,639*	-$3,766***	-$2,236 (ns)	nr USD	100%
Hansen 2012 [26]	Medicaid	'04 –'08	87,015	1 year	All health care	PDC>=0.8; PDC<0.8	$4,603[f]	-$5,539[f]	-$5,701[f]	2008 USD	100%
Robertson 2014 [27]	Medicaid	'02 –'08	1,367	Unclear mean 65 months	Mental health care, crime including arrest and incarceration	MPR>=0.8 for 31-60d vs 61-90d in 90d	-$2,100	-$1,848	-$6,348	nr USD	84%
						MPR>=0.8 for 1-30d vs 61-90d in 90d	-$792	-$3,084	-$6,984		
						MPR>=0.8 for 0d vs 61-90d in 90d	-$6,576	-$4,332	-$15,552		
Roberto 2017 [40]	Medicare	'11-'12	13,681	2nd year	Hospital costs	PDC>=0.90 vs PDC<0.70	-$888***[g]	nr	nr	2012[h] USD	100%
						PDC 0.80-0.89 vs PDC<0.70	-$723**[g]	nr	nr		
						PDC 0.70-0.79 vs PDC<0.70	-$544[g]	nr	nr		
Joe 2016 [41]	Korean Insurance	2011	7,848	Mean 320d	Psychiatric and medical care costs	MPR>=0.8 vs MPR<0.8	Nr	nr	843,000	2011 KRW	100%
						Treat. gap>56d vs gap<=56d	Nr	nr	948,000		

van der Lee 2016 [42]	Dutch insurance	'09-'11	7,392	3 years	All health care	3 years cont. care[i] vs 2 years	€12,328	-€699	€9,341	2009-2011[j] Euro	100%
						3 years cont. care[i] vs 1 year	€10,782	-€997	€5,700		
						3 years cont. care[i] vs 0 years	€5,808	-€1,143	-€1,067		
Database analysis - Switchers analysed separately											
McCombs 2000 [28]	Medicaid	'87 –'96	2,476	2 years	All health care	cont. treat. vs treat. gap>44d	$697[k,l]	-$173[l]	-$111[l]	1996 USD	100%
						cont. treat. vs no treat.	$4,711[k,l]	-$283[l]	$5,306[l]		
Pai 2010[#] [29]	Medicaid	'94 –'03	nr	nr	nr	Persistent vs intermittent	nr	nr	-$1,791***	nr USD	100%
						Persistent vs quitters	nr	nr	-$1,484***		
						Persistent vs partial augmenters	nr	nr	$1,935***		
						Persistent vs full augmenters	nr	nr	$3,185***		
Ahn 2008 [30]	Medicaid	'94 –'03	36,195	1 year	All health care	adherent vs switchers	$701***[k]	$1,086***	$3,654***	nr USD	100%
						Adherent vs non-adherent	$559***[k]	-$1,678***	-$408***		
Database analysis - Overfillers analysed separately											
Gilmer 2004 [31]	Medicaid	'98 –'00	1,619	1-3 year	All health care	MPR <0.5 vs 0.8-1.1	$2,388***	-$2,921***	-$1,337***	nr USD	100%
						MPR 0.5-0.79 vs 0.8-1.1	$1,664***	-$1,321***	-$102 (ns)		
						MPR>1.1 vs 0.8-1.1	$1,447***	$1,172***	$4,539***		
Eaddy 2005 [32]	Medicaid	'99 –'01	7,864	1 year	Disease specific	CMA<0.8 vs 0.8-1.25	$1,788***[m]	-$912[m] (ns)	$708[m] (ns)	2001/ 2002 USD	nr[n]
						CMA>1.25 vs 0.8-1.25	$7,260[m] (ns)	$732[m] (ns)	$8616[m] (ns)		
Dilokthorn-sakul 2016 [43]	Hospital database Thailand	'11-'13	582	2 years[o]	All care billed by hospital	MPR<0.8 vs 0.8-1.2	nr	nr	$143[p] (ns)	2013 USD	100%
						MPR>1.2 vs 0.8-1.2	nr	nr	$116[p] (ns)		
Database analysis - use of quasi-experimental design or analysis to control for unobserved confounding											
Zeber 2007 [39]	VA	'00 –'03	80,637	40 months	All drugs and psych. hosp.	Effect of higher drug copay: exempt vs non-exempt	nr	-$133***[q]	nr	1999 USD	100%
Farley 2010 [33]	Medicaid	'01-'03	16,582	2 years[r]	Mental health care	PDC and treatment gap>90d	nr	-$46***[s]	-$21*	nr USD	100%

Jiang 2015 [34]	Medicaid + private	'07 –'13	32,374	2nd year	All health care	PDC>=0.8; PDC<0.8	$27,664 ***	-$8,194***	$19,497*	2013 USD	40%[t]
						Time to drug gap >15d of >360d; <360	$34,178 ***	-$10,278 ***	$23,927*		
Other database analyses											
Marcus 2008 [35]	Medicaid	'01 –'03	35,815	variable	Disease specific	Any drug treatment 15 days before hospitalization (Y/N)	nr	nr	nr	2005 USD	100%
Markowitz 2013 [36]	Medicaid	'04 –'08	2,541	18 months	All health care	PDC>=0.8; PDC<0.8	nr	nr	nr	2010 USD	100%
Cohort studies											
Knapp 2004 [45]	survey	'93-'94	658	1 year	All health & day care[u]	Self-report	£2,500 (ns)	nr	£5,000 (ns)	2001 GBP	68%
Salize 2009 [46]	MECCA RCT	'02-'05	507	1 year	Mental health care	'drug compliance' data collected	nr	8% (ns), 40%*[v]	-6% (ns), -18%*[w]	2004 PPP Euros	84%
Novick 2010 [49]; Hong 2010 [47]	SOHO study	'00-'04	5,364	3 years	Disease specific	Physician interview: full adhere. vs partial adhere.	nr	nr	£202	nr GBP	100%
						Physician interview: full adhere. vs non adhere.	£1024	nr	£952		
King 2010 [50]; King 2014 [48]	QUATRO RCT	'02-'03	409	1 year	All costs[x]	Morisky scale: 0-2 vs 3-4	nr	nr	-€6,380[y] (ns)	2003 PPP Euros	100%

adhere. – adherence; admin. – administrative; AMQ – attitude to medication questionnaire; augment. – augmentation of treatment; CMA – Continuous medications available; CMR Continuous multiple interval Medication Availability; d – days; discont. – discontinuation; DAI – drug attitude inventory; GBP – British Pound; hosp. – hospitalization; KRW – South Korean Won; mod. – moderate; MPR – Medication Possession Ratio; nr – not reported; ns – not statistically significant; observ. – observation; PDC – Proportion of days covered; PPP – Purchasing Power Parity; psych. – psychiatric; QUATRO – The Quality of Life following Adherence Therapy for People Disabled by Schizophrenia and their Carers study; quart. – quartile; RCT - Randomised Controlled Trial; SES – Service Engagement Scale; sev. – severe; SOHO – Schizophrenia Outpatient Health Outcomes; treat. – treatment; USD - United States Dollar; VA – Veterans Health Administration; X survey – cross-sectional survey. [#]Annualised mean costs for patients in category identified minus annualised mean costs for patients in category including full adherence (as opposed to excess fillers where identified). Data for schizophrenia patients reported where available. [#] Conference Abstract. * p<0.05. ** p<0.01. *** p<0.001. [a]Including schizo-affective disorder. [b]Data not consistently reported in paper. [c]Cost data reported

for subgroup of patients with schizophrenia. [d]Costs of arrests and involuntary assessments included. [e]Data reported is weighted mean across patients prescribed typical, atypical and both antipsychotics. [f]Means calculated after averaging data across adherence categories for cardio-metabolic drugs. [g]Cost differences reported with respect to lowest adherence category (PDC<0.7). [h]Price year not explicitly reported. [i]Continuous care defined as a year with outpatient psychiatric care and/or at least 180 days of antipsychotic medication. [j]Costs appear to be summed over period 2009-2011 without adjustment for inflation. [k]Psychiatric hospitalisation costs. [l]Costs derived after combining reported regression coefficients assuming the base category to be no treatment and that the 'received drug treatment' category including patients with and without treatment gaps. [m]Reported cost differences are unadjusted; significance determined from regression analysis adjusting for baseline differences. [n]Population includes all patients prescribed antipsychotics. [o]Adherence assessed in first year, costs in second year. [p]Reported costs are 'only direct medical cost incurred in the hospital' – it is not clear if the costs include drug treatment. [q]Calculated as the difference in difference between pharmacy costs reported in Table 2 of the paper for the exempt and the copayment eligible group for the periods before and after the change in copayment; significance determined from regression analysis of the natural logarithm of pharmacy costs. [r]12 month pre-test, 12 month post-test design. [s]Non-psychiatric medications. [t]Proportion includes some patients diagnosed with both schizophrenia and bipolar disorder. [u]Costs included health care, social care, day care and sheltered employment. [v]8% increase in psychotropic drug costs (gamma model) and 40% increase in costs (log-normal model) associated with a change in compliance from good to average or from average to poor at baseline. [w]6% decrease in total costs (log-normal model) and 18% decrease in costs (gamma model) with a change in compliance from good to average or from average to poor at baseline. [x]Societal perspective included health care, social care, criminal justice, informal care and productivity costs. [y]Reduction in costs for a change from adherent to non-adherent for a white European man, aged 45, without tertiary education and resident in London.

Table 1. Analyses of administrative data

Reference	Interv-ention	No. of pati-ents	Follow-up period	Measure of adherence	Impact of intervention on compliance	Annualised difference in costs between intervention and control arms (statistical significance)[#]			Price Year	Patients with schizo-phrenia
						hospital	Drugs	total		
Healey 1998 [51]; Kemp 1998 [52]	Compliance therapy	47	18 months	Interview – seven point scale	Significant increase in intervention arm	nr	nr	-£939[a] (ns)	1995/6 GBP	nr
Stant 2007 [53]; Wunderlink 2007 [54]	Guided discontinuation of APs	128	18 months	Randomised to discontinuation	discontinuation: treatment, 54%; control, 8%	-€3,425[b] (ns)	-€394[b] (ns)	-€4,769[b] (ns)	2004 Euros	45%
Gilden 2011 [55]; Staring 2010 [56]	Adherence therapy	109	1 year	Compliance subscale of SES and interview	Significant increase in intervention arm	-€2,300[c] (ns)	nr	€514[d] (ns)	2008 Euros	100%
Henderson 2015 [57]; Priebe 2016 [58]	Financial incentive	141	1 year	Proportion of depot prescriptions received	Increase in intervention arm 11.5% (p = 0.003)	-£1,698[e] (ns)	£177[f] (ns)	£699[g] (ns)	2010/11 GBP	92%

[#]treatment effect of intervention; APs – Antipsychotic medication; GBP – British Pounds; nr – not reported; ns – not statistically significant; SES – Service Engagement Scale; [a]Calculated from weekly unadjusted difference between Intervention and control over 18 months. [b]Calculated from unadjusted difference between Intervention and control over 18 months following initiation of discontinuation in the treatment group. [c]Psychiatric and non-psychiatric hospital costs. [d]Intervention costs include Adherence therapy costs of €726 per patient. [e]Mental health related hopsitalization costs. [f]Sum of difference in costs for oral medications (data available for 133 patients) and depot medications (data available for 131 patients). [g]Intervention costs include financial incentives of £303 per patient.

Table 2. Trials of interventions to modify adherence

Figures

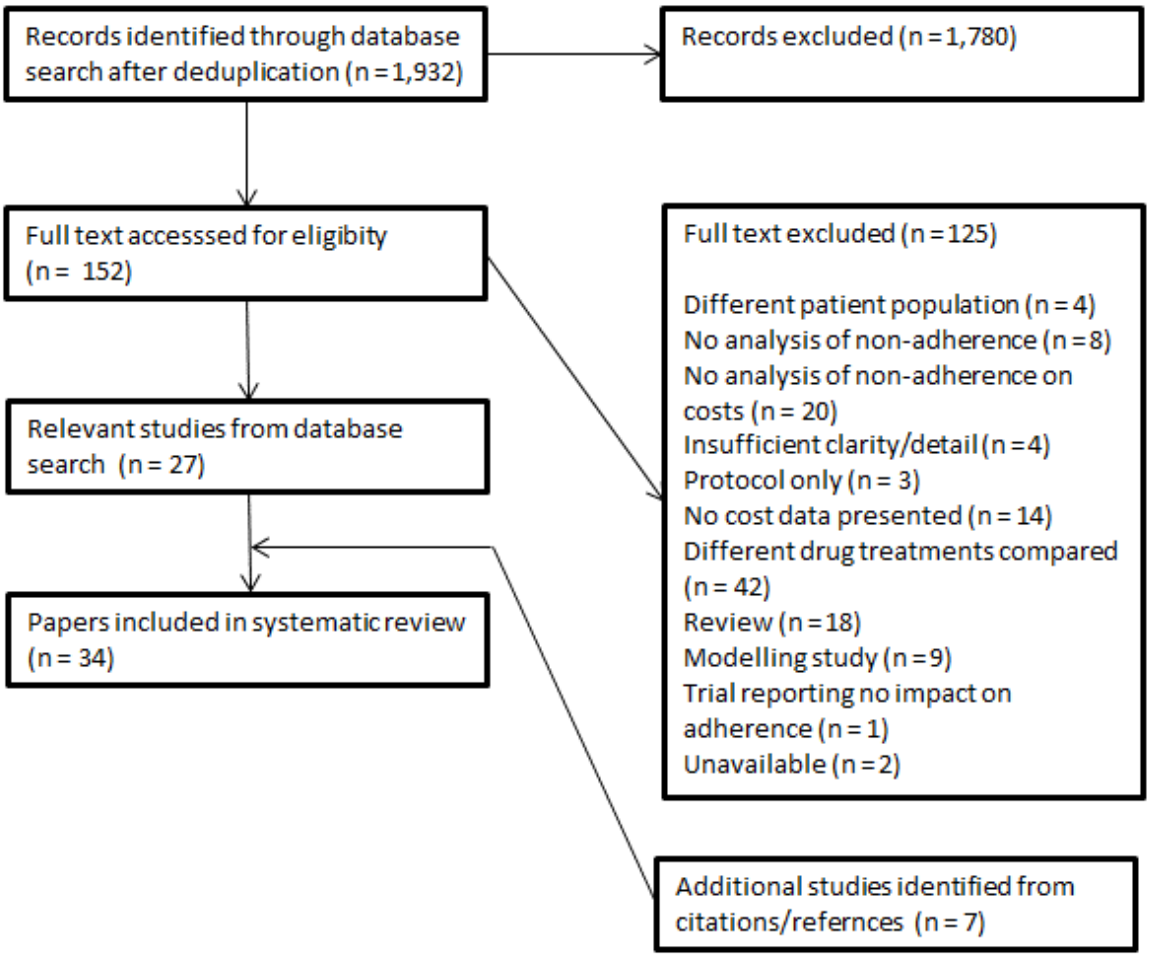

Figure 1. Search results and literature selection

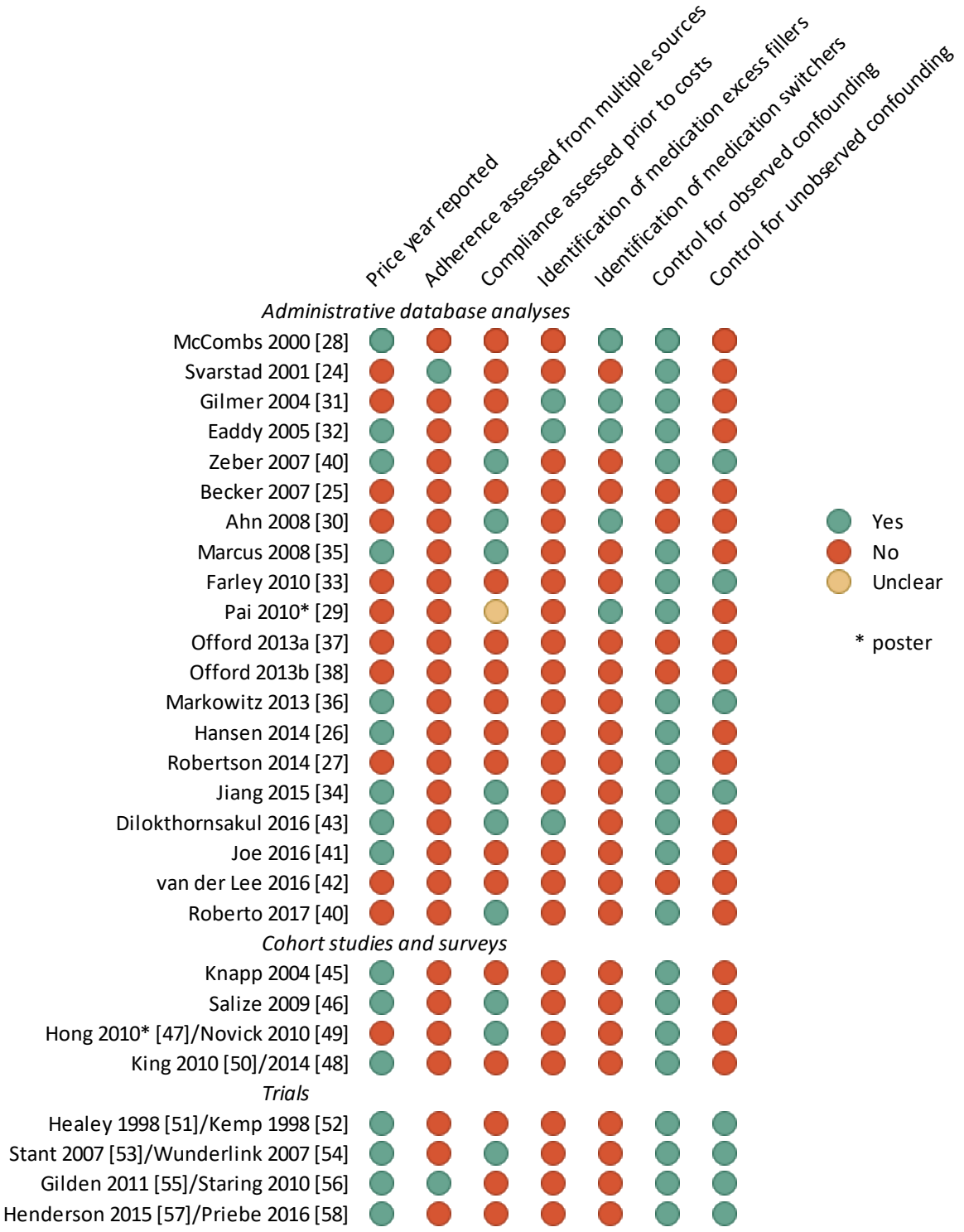

Figure 2. Assessment of quality of included studies